```
=> d que
L5          74 SEA (CEREBR? OR BRAIN)(2A)(BIOAVAIL? OR BIOLOGICAL AVAIL?)(5A)(
               INCREAS? OR ENHANC?)
L6          24 SEA L5 AND (ARGININE OR NADPH OR TETRAHYDROBIOPTERIN OR ECNOS
               OR ENOS OR NO OR NITRIC OXIDE OR NITROGEN MONOXIDE)
L7           7 DUP REM L6 (17 DUPLICATES REMOVED)
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=> d ibib ab hitind 1-7

L7 ANSWER 1 OF 7 USPATFULL
ACCESSION NUMBER: 2002:259378 USPATFULL
TITLE: Methods for enhancing the bioavailability of a drug
INVENTOR(S): Hayward, Neil J., North Grafton, MA, UNITED STATES
Gefter, Malcolm L., Lincoln, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002142950	A1	20021003
APPLICATION INFO.:	US 2001-781133	A1	20010209 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-181833P	20000211 (60)
	US 2000-181943P	20000211 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: LAHIVE & COCKFIELD, 28 STATE STREET, BOSTON, MA, 02109
NUMBER OF CLAIMS: 65
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Page(s)
LINE COUNT: 2566
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides methods and compositions for enhancing the bioavailability of a drug in a subject. The present invention also provides methods and compositions for treating or preventing hepatic injury in a subject in need thereof. The invention further provides methods for identifying hydrophobic peptides, e.g., .beta.-amyloid peptide derivatives, which are useful in enhancing bioavailability of a drug in a subject.

L7 ANSWER 2 OF 7 USPATFULL
ACCESSION NUMBER: 2002:251808 USPATFULL
TITLE: Delivery systems and methods for noscapine and noscapine derivatives, useful as anticancer agents
INVENTOR(S): Joshi, Harish C., Decatur, GA, UNITED STATES
Ye, Keqiang, Lilburn, GA, UNITED STATES
Kapp, Judith, Atlanta, GA, UNITED STATES
Landen, Jaren, Decatur, GA, UNITED STATES
Archer, David, Roswell, GA, UNITED STATES
Armstrong, Cheryl, Winnetka, IL, UNITED STATES
Liu, Fuqiang, Edison, NJ, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002137762	A1	20020926
APPLICATION INFO.:	US 2002-56913	A1	20020125 (10)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 2000-582375, filed on 26 Sep 2000, GRANTED, Pat. No. US 6376516		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-57037P	19970819 (60)
	US 2001-264357P	20010126 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: JOHN S. PRATT, ESQ, KILPATRICK STOCKTON, LLP, 1100 PEACHTREE STREET, SUITE 2800, ATLANTA, GA, 30309
NUMBER OF CLAIMS: 22
EXEMPLARY CLAIM: 1
LINE COUNT: 1204
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to methods useful for the treatment of neoplastic diseases, tumor cells, and the treatment of cancer delivering compounds of the formula ##STR1##

The invention provides various methods of delivering such compounds, combinations of treatments, and altering such compounds to enhance their effectiveness.

L7 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:688084 CAPLUS
DOCUMENT NUMBER: 133:271636
TITLE: **Increasing cerebral bioavailability** of drugs by stimulating **increased** production of **nitric oxide**.
INVENTOR(S): Moskowitz, Michael A.; Liao, James K.; Ron, Eyal S.; Omstead, Mary Nallin
PATENT ASSIGNEE(S): Enos Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000056328	A1	20000928	WO 2000-US7089	20000320
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1175210	A1	20020130	EP 2000-919452	20000320
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002539257	T2	20021119	JP 2000-606233	20000320

PRIORITY APPLN. INFO.:
US 1999-139484P P 19990319
US 1999-138578P P 19990611
US 1999-155485P P 19990923
WO 2000-US7089 W 20000320

AB A method and compns. are provided for **increased cerebral bioavailability** of blood-born compns. by administering the compn. of interest while increasing brain **NO** levels. This increase in **NO** levels may be accomplished by stimulating increased prodn. of

NO by endothelial **NO** synthase (**eNOS**), esp. by administering L-**arginine**, by administering agents that increase **NO** levels independent of **ecNOS**, or by any combination of these methods. As **NO** is increased, cerebral blood flow is consequently increased, and drugs in the blood stream are carried along with the increased flow into brain tissue. By increased flow, the site of action will be exposed to more drug mols. By stimulating increased **NO** prodn., administration of drugs that are not easily introduced to the brain may be facilitated and/or the serum concn. necessary to achieve desired physiol. effects may be reduced. Examples were given showing the effect of L-**arginine** on cerebral blood flow and compns. contg. L-**arginine** and simvastatin.

IC ICM A61K031-195
ICS A61K031-519

CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 1

ST brain drug bioavailability **nitric oxide**; **arginine** brain drug bioavailability

IT **Brain**
Drug **bioavailability**
(**increasing cerebral bioavailability** of drugs by stimulating **increased** prodn. of **nitric oxide**.)

IT Brain, disease
(stroke, ischemic; **increasing cerebral bioavailability** of drugs by stimulating **increased** prodn. of **nitric oxide**.)

IT 10102-43-9, **Nitric oxide**, biological studies
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(**increasing cerebral bioavailability** of drugs by stimulating **increased** prodn. of **nitric oxide**.)

IT 74-79-3, L-**Arginine**, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**increasing cerebral bioavailability** of drugs by stimulating **increased** prodn. of **nitric oxide**.)

IT 533-45-9, Clomethiazole 77086-22-7, MK-801 79902-63-9, Simvastatin 139639-23-9, Tissue plasminogen activator 171049-14-2, Lotrafiban
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**increasing cerebral bioavailability** of drugs by stimulating **increased** prodn. of **nitric oxide**.)

IT 125978-95-2, **Nitric oxide** synthase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**increasing cerebral bioavailability** of drugs by stimulating **increased** prodn. of **nitric oxide**.)

IT 53-57-6, **Nadph** 17528-72-2, **Tetrahydrobiopterin**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**increasing cerebral bioavailability** of drugs by stimulating **increased** prodn. of **nitric**

oxide.)
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
ACCESSION NUMBER: 2000:31124 BIOSIS
DOCUMENT NUMBER: PREV200000031124
TITLE: Antinociceptive and hemodynamic effects of a novel alpha2-adrenergic agonist, MPV-2426, in sheep.
AUTHOR(S): Eisenach, James C. (1); Lavand'homme, Patricia; Tong, Chuanyao; Cheng, Jen-Kun; Pan, Hui-Lin; Virtanen, Raimo; Nikkanen, Hanna; James, Robert
CORPORATE SOURCE: (1) Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC, 27157-1009 USA
SOURCE: Anesthesiology (Hagerstown), (Nov., 1999) Vol. 91, No. 5, pp. 1425-1436.
ISSN: 0003-3022.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Background: alpha2-Adrenergic agonists produce analgesia primarily by a spinal action and hypotension and bradycardia by actions at several sites. Clonidine is approved for epidural use in the treatment of neuropathic pain, but its wider application is limited by hemodynamic side effects. This study determined the antinociceptive and hemodynamic effects of a novel alpha2-adrenergic agonist, MPV-2426, in sheep. Methods: Forty sheep of mixed Western breeds with indwelling catheters were studied. In separate studies, antinociception to a mechanical stimulus, hemodynamic effects, arterial blood gas tensions, cerebrospinal fluid pharmacokinetics, and spinal cord blood flow was determined after epidural, intrathecal, and intravenous injection of MPV-2426. Results: MPV-2426 produced antinociception with greater potency intrathecally (ED50 = 49 mug) than epidurally (ED50 = 202 mug), whereas intravenous administration had **no** effect. Intrathecal injection, in doses up to three times the ED95,failed to decrease systemic or central arterial blood pressures or heart rate, whereas larger doses, regardless of route, **increased** systemic arterial pressure. **Bioavailability** in **cerebrospinal** fluid was 7% after epidural administration and 0.17% after intravenous administration. Intrathecal MPV-2426, in an ED95 dose and three times this dose, produced a dose-independent reduction in thoracic and lumbar spinal cord blood flow. Conclusions: MPV-2426 shares many characteristics of other alpha2-adrenergic agonists examined in sheep, but differs from clonidine and dexmedetomidine by lack of antinociception and minimal reduction in oxygen partial pressure after large intravenous and epidural injections. **No** hemodynamic depression was observed after intrathecal injection at antinociceptive doses. These results suggest this compound may be an effective spinal analgesic in humans with less hypotension than clonidine, although its relative potency to cause sedation was not tested in this study.

CC Pharmacology - General *22002
Biochemistry - Gases *10012
Biochemical Studies - General *10060
Metabolism - General Metabolism; Metabolic Pathways *13002
Cardiovascular System - General; Methods *14501
Blood, Blood-Forming Organs and Body Fluids - Other Body Fluids *15010
Nervous System - General; Methods *20501
BC Bovidae 85715

Hominidae 86215
IT Major Concepts
Nervous System (Neural Coordination); Pharmacology
IT Parts, Structures, & Systems of Organisms
cerebrospinal fluid: nervous system
IT Chemicals & Biochemicals
MPV-2426: alpha-2-adrenergic agonist, analgesic - drug, antinociceptive effect, hemodynamic effect, intravenous injection, pharmacokinetics; oxygen: partial pressure
IT Miscellaneous Descriptors
antinociception; heart rate
ORGN Super Taxa
Bovidae: Artiodactyla, Mammalia, Vertebrata, Chordata, Animalia; Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae); sheep (Bovidae)
ORGN Organism Superterms
Animals; Artiodactyls; Chordates; Humans; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Primates; Vertebrates
RN 7782-44-7 (OXYGEN)

L7 ANSWER 5 OF 7 COPYRIGHT 2002 Gale Group

ACCESSION NUMBER: 1998:166461 NLDB
TITLE: EMERGING TECHNOLOGIES: Therapy Changing for Congestive Heart Failure
SOURCE: Genesis Report-Rx, (1 Apr 1998) Vol. 7, No. 3. ISSN: 1061-2270.
PUBLISHER: Genesis Group Associates, Inc
DOCUMENT TYPE: Newsletter
LANGUAGE: English
WORD COUNT: 5166

L7 ANSWER 6 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
ACCESSION NUMBER: 1997:348652 BIOSIS
DOCUMENT NUMBER: PREV199799647855
TITLE: Interactions between **nitric oxide** and dopamine in inhibitory learning and memory in newborn rate.
AUTHOR(S): Myslivecek, J. (1); Barcal, J.; Hassmannova, J.; Zahlava, J.; Zalud, V.
CORPORATE SOURCE: (1) Inst. Pathophysiol., Charles Univ., Med. Fac. Plzen, CZ-301 66 Plzen Czech Republic
SOURCE: Neuroscience, (1997) Vol. 79, No. 3, pp. 659-669. ISSN: 0306-4522.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Taking into account our previous results on dopamine and **nitric oxide** effects on neonatal inhibitory learning and memory in rats, the mutual interactions of the two molecules were studied in this experimental paradigm. Both **increased** dopamine content and **nitric oxide bioavailability** in the **brain** after application of dopamine and L-**arginine** as substrate for **nitric oxide** synthase solutions into lateral cerebral ventricles improved learning and 24 h memory. Joint application of dopamine and L-**arginine** yielded still more improvement. Learning and memory processing were dose dependently enhanced by D-1 receptor agonists as well, whereas D-1 receptor antagonists had an

opposite and also dose-dependent effect. Dopamine or D-1 receptor agonists administered together with nitro-L-**arginine**, a **nitric oxide** synthase inhibitor that impaired learning and memory due to a decreased **nitric oxide** availability, antagonized the effect of nitro-L-**arginine**, as did L-**arginine**. D-1 receptor antagonists impaired both learning and memory, and L-**arginine** rendered learning values normal. The dopamine and D-1 receptor-agonist effect on 24 h memory was concentration dependent, and their higher concentrations substantially increased the retention indexes. The intimate mechanisms of these interactions are to be identified in further experiments.

CC Behavioral Biology - Animal Behavior *07003
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
Biophysics - Membrane Phenomena *10508
Enzymes - Physiological Studies *10808
Cardiovascular System - Physiology and Biochemistry *14504
Endocrine System - Neuroendocrinology *17020
Nervous System - Physiology and Biochemistry *20504

BC Muridae *86375

IT Major Concepts
Behavior; Biochemistry and Molecular Biophysics; Cardiovascular System (Transport and Circulation); Endocrine System (Chemical Coordination and Homeostasis); Enzymology (Biochemistry and Molecular Biophysics); Membranes (Cell Biology); Nervous System (Neural Coordination)

IT Chemicals & Biochemicals
NITRIC OXIDE; DOPAMINE; **NITRIC OXIDE** SYNTHASE

IT Miscellaneous Descriptors
BRAIN; DOPAMINE; D1 RECEPTOR; LEARNING; MEMORY; NERVOUS SYSTEM; NEWBORN; **NITRIC OXIDE**; **NITRIC OXIDE** SYNTHASE

ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
rat (Muridae)

ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates; rodents; vertebrates

RN 10102-43-9 (**NITRIC OXIDE**)
51-61-6 (DOPAMINE)
125978-95-2 (**NITRIC OXIDE** SYNTHASE)

L7 ANSWER 7 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3
ACCESSION NUMBER: 1995:272102 BIOSIS
DOCUMENT NUMBER: PREV199598286402
TITLE: Routes of administration and effect of carbidopa pretreatment on 6-(18F)fluoro-L-dopa/PET scans in non-human primates.
AUTHOR(S): Chan, Grace L.-Y. (1); Doudet, Doris J.; Dobko, Teredsa; Hewitt, Kellie A.; Schofield, Poppy; Pate, Brian D.; Ruth, Thomas J.
CORPORATE SOURCE: (1) PET, Acute Care Unit, Univ. Hosp., UBC Site, 2211 Wesbrook Mall, Vancouver, BC V6T 3B5 Canada
SOURCE: Life Sciences, (1995) Vol. 56, No. 21, pp. 1759-1766. ISSN: 0024-3205.
DOCUMENT TYPE: Article

LANGUAGE: English

AB In 6-(18F)fluoro-L-dopa (Fdopa)/positron emission tomography (PET) studies, carbidopa pretreatment **increases** the Fdopa **bioavailability** to the **brain** and **enhances** the intensity of striatal PET images. Different PET research teams have used various carbidopa doses and routes of administration in non-human primate studies. The purpose of this study was to examine the plasma profiles of carbidopa and the effect of the route of administration of carbidopa on a Fdopa/PET scan. Cynomolgus monkeys were given carbidopa either orally (5 mg/kg), intraperitoneally (2.5 and 5 mg/kg) or intravenously (5 mg/kg) 60-90 min prior to the Fdopa injection. Carbidopa-treated monkeys were compared to monkeys without carbidopa treatment. **No** carbidopa was detected in the plasma samples when it was given orally, possibly due to poor absorption in the gastrointestinal tract. In addition, the striatal and cortical activities were not statistically different from those of the untreated monkeys, indicating that little or **no** inhibition of the peripheral decarboxylation of Fdopa by carbidopa had taken place. When carbidopa was given intraperitoneally at a dose of 2.5 and 5 mg/kg and intravenously at 5 mg/kg, plasma carbidopa concentrations at the time of Fdopa injection were 0.95 +- 0.26, 2.22 +- 0.23 and 2.79 +- 0.26 mu-g/ml, respectively. Because of inhibition of peripheral decarboxylation of Fdopa by carbidopa, more Fdopa was available for transport into the brain and as a result, both the striatal and cortical activities were significantly higher than those of the untreated monkeys. Carbidopa administration had **no** effect on either the striatal-to-cortical activity ratio or the striatum uptake value.

CC Biochemical Studies - General 10060
Movement *12100
Pathology, General and Miscellaneous - Diagnostic *12504
Metabolism - Proteins, Peptides and Amino Acids *13012
Digestive System - General; Methods *14001
Cardiovascular System - General; Methods *14501
Coelomic Membranes; Mesenteries and Related Structures *18200
Dental and Oral Biology - General; Methods *19001
Nervous System - General; Methods *20501
Nervous System - Physiology and Biochemistry *20504
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Pharmacology - Clinical Pharmacology *22005
Pharmacology - Neuropharmacology *22024
Routes of Immunization, Infection and Therapy *22100

BC Cercopithecidae *86205

IT Major Concepts
Cardiovascular System (Transport and Circulation); Dental and Oral System (Ingestion and Assimilation); Digestive System (Ingestion and Assimilation); Metabolism; Methods and Techniques; Morphology; Nervous System (Neural Coordination); Pathology; Pharmacology; Physiology

IT Chemicals & Biochemicals
CARBIDOPA

IT Miscellaneous Descriptors
AUTONOMIC-DRUG; BIOAVAILABILITY; BRAIN TRANSPORT; CARBIDOPA; DIAGNOSTIC METHOD; DIAGNOSTIC-DRUG; DRUG ADMINISTRATION ROUTE COMPARISON; ENHANCED IMAGE INTENSITY; INTRAPERITONEAL ROUTE; INTRAVENOUS ROUTE; ORAL ROUTE; PHARMACOKINETICS; 6-FLUORINE-18- FLUORO-L-DOPA

ORGN Super Taxa
Cercopithecidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
cynomolgus monkey (Cercopithecidae)

ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman primates; nonhuman vertebrates; primates; vertebrates
RN 28860-95-9 (CARBIDOPA)